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Ezetimibe improves postprandial hyperlipemia and its induced endothelial dysfunction

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ABSTRACT

Objective: Postprandial hyperlipemia has been shown to impair endothelial function and contribute to the development of atherosclerosis. We investigated the association between postprandial lipid profiles and endothelial function, and we examined the effects of ezetimibe on postprandial hyperlipemia and lipemia-induced endothelial dysfunction.
Methods: A randomized prospective trial in which 10 mg/day of ezetimibe was administered to 10 subjects for 4 weeks and not administered to 10 subjects (control group) was performed. Lipid profiles and endothelial function, assessed by brachial artery flow-mediated dilation (FMD) during a fasting state and at 2, 4, 6 and 8 h after an oral cookie loading test, were determined before and after treatment for 4 weeks.
Results: In all subjects before treatment, the maximum reduction in postprandial %FMD was significantly correlated with the maximum increases in postprandial triglyceride (TG) ($r = -0.499$, $P < 0.05$) and apolipoprotein B-48 (apoB-48) concentrations ($r = -0.551$, $P < 0.05$). Ezetimibe treatment for 4 weeks significantly suppressed postprandial elevation in TG (area under the incremental curve, from 1419 ± 594 to 968 ± 321 mg h/dl, $P < 0.05$), remnant lipoprotein cholesterol (from 66.9 ± 27.6 to 38.9 ± 15.4 mg h/dl, $P < 0.01$) and apoB-48 (from 58.8 ± 27.5 to 36.2 ± 17.0 μg h/ml, $P < 0.05$) concentrations, and postprandial endothelial dysfunction assessed by %FMD (maximum reduction in %FMD, from $-2.6 \pm 1.1\%$ to $-1.2 \pm 0.8\%$, $P < 0.05$), whereas no significant changes were observed in the control group.
Conclusion: Postprandial hyperlipemia is closely correlated with transient endothelial dysfunction. Ezetimibe improves postprandial hyperlipemia and its induced endothelial dysfunction.

1. Introduction

A large number of studies have demonstrated that postprandial hyperlipemia contributes to the development of atherosclerosis and coronary heart disease (CHD) [1–3]. Postprandial lipemia is a physiological phenomenon occurring several times a day after ingestion of dietary fat when the dietary sources of fat exceeded the actual needs. Disturbances of triglyceride (TG) metabolism also induce prolonged postprandial hyperlipemia. Patients with obesity, diabetes and metabolic syndrome often have postprandial hyperlipemia [4] and exaggerated postprandial hyperlipemia has been observed even in fasting normolipidemic subjects [5]. In such circumstances, TG-rich lipoproteins (TRLs), which consist of chylomicrons assembled by TG, dietary cholesterol and apolipoprotein B-48 (apoB-48), have been shown to induce endothelial dysfunction, an initial process of atherogenesis, through enhanced inflammation and oxidative stress. Norata et al. showed that postprandial TRLs upregulate the expression of pro-inflammatory cytokines, inducing the impairment of brachial artery endothelial function beyond 8 h postprandially in both hyperlipidemic and normolipidemic subjects [6]. Moreover, van Oostrom et al. demonstrated that postprandial lipemia contributes to the recruitment of neutrophils with concomitant production of pro-inflammatory cytokines and oxidative stress, resulting in endothelial dysfunction in healthy normolipidemic subjects [7]. Thus, even in healthy volunteers, postprandial lipemia has been associated with the activation of leukocytes and upregulation of pro-inflammatory cytokines on the endothelium. Actually, several studies have demonstrated that postprandial hyperlipemia caused by oral fat intake induces impairment of flow-mediated dilations (FMD) of the brachial artery in healthy volunteers [8,9].

Ezetimibe, a novel lipid-lowering drug that selectively inhibits cholesterol absorption by inhibiting Niemann-Pick C1 like 1 (NPC1L1) protein, is commonly used for treatment of dyslipidemia. Recently, a clinical trial by Masuda et al. reported that ezetimibe improves fasting and postprandial hyperlipemia by suppression of

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intestinal chylomicron production in patients with type IIb hyperlipemia [10]. However, the effect of ezetimibe monotherapy on postprandial hyperlipemia-induced endothelial dysfunction was not fully evaluated.

Accordingly, the aim of the present study was to determine the association between postprandial lipid profiles and endothelial function, and to determine the effects of ezetimibe monotherapy on postprandial hyperlipemia and lipemia-induced endothelial dysfunction.

2. Methods

2.1. Study populations

Twenty volunteers, including 17 men and 3 women, were enrolled in this study. The inclusion criteria were aged of 20 years or above and not receiving lipid-lowering medications. Subjects were excluded from the study if they had undergone major surgery within 3 months prior to enrollment or if they had concomitant inflammatory diseases or malignant tumors. A randomized prospective trial in which ezetimibe (10 mg/day) was administered to 10 subjects for 4 weeks (ezetimibe group) and not administered to 10 subjects (control group) was performed. Lipid profiles and endothelial function, assessed by brachial artery FMD during a fasting state and at 2, 4, 6 and 8 h after an oral cookie loading test, were determined before and after treatment for 4 weeks. None of the 20 subjects had hypertension, diabetes, or cerebrovascular or cardiovascular disease, but 9 subjects met the diagnostic criteria for dyslipidemia, one subject met the criteria for metabolic syndrome, and 11 subjects were previous or current smokers. None of the subjects had received any medications. Hypertension was diagnosed according to the 1999 World Health Organization-International Society of Hypertension Guideline [11]. Diabetes was defined as a fasting blood glucose level $\geq$126 mg/dl and hemoglobin A1c (HbA1c) $\geq$6.1%. Dyslipidemia was diagnosed according to the 2007 Japan Atherosclerotic Society Guideline [12]. Metabolic syndrome was defined as waist circumference $\geq$85 cm for men or $\geq$90 cm for women as an essential component combined with 2 or more of the following components according to the 2005 definition and diagnostic criteria of metabolic syndrome in Japanese: TG $\geq$150 mg/dl and/or high-density lipoprotein cholesterol (HDL-C) <40 mg/dl; systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$85 mmHg; fasting blood glucose $\geq$110 mg/dl.

All of the studies were approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, and written informed consent was obtained from all subjects before the procedure.

2.2. Study protocol

2.2.1. Oral fat load (cookie test)

For fat loading, a cookie test was performed after overnight fasting for at least 8–12 h. The cookie consisted of 75 g carbohydrate (flour starch and maltose), 28.5 g fat (butter) and 8 g protein for a total of 592 kcal a carton (SARAYA Corp, Osaka, Japan) [13,14]. Subjects are given 30 g fat/m^2 body surface area, and they are instructed to ingest the cookie with water within 20 min. Time measurement was started when half of the cookie had been ingested. Venous blood samples were drawn and endothelium-dependent vascular function, assessed by FMD of the brachial artery, was determined during the fasting state before cookie ingestion and at 2, 4, 6 and 8 h after the cookie load. Endothelium-independent dilation, assessed by nitroglycerin-mediated dilation (NMD), was also measured during the fasting state before cookie ingestion and at 4 and 8 h after the cookie load. Measurements of FMD and NMD were performed by the same skillful technician who was blinded to the study design and medication status.

2.2.2. Biochemical analysis

The following parameters during the fasting state before cookie ingestion were measured: serum total cholesterol (Total-C), TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, malondialdehyde-modified (MDA)-LDL cholesterol, remnant lipoprotein cholesterol (RLP-C), apoB-48, adiponectin, monocyte chemotactic protein-1 (MCP-1) and plasma glucose levels. HbA1c levels were measured using a high-performance liquid chromatography (HPLC) method. Concentrations of fasting plasma insulin were measured using a chemiluminescent enzyme immunoassay (CLEIA) method. Lipid profiles and other markers were measured at SRL Co., Ltd., Tokyo, Japan. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [fasting plasma glucose (mg/dl) $\times$ fasting plasma insulin (μIU/ml)/405] and glucose intolerance was defined as HOMA-IR $\geq$2.0. Serum Total-C, TG, LDL-C, MDA-LDL, RLP-C, apoB-48 and plasma glucose levels were measured at 2, 4, 6 and 8 h after the cookie load. To compare the postprandial changes before and after treatment for 4 weeks in these parameters, area under the curve (AUC) was calculated using the trapezoidal method.

2.3. Assessment of endothelial vasomotor function

Endothelium-dependent and -independent dilations were assessed as parameters of vasodilation according to the guidelines for ultrasound assessment of FMD of the brachial artery [15]. Using a 10-MHz linear array transducer probe (Unex Co. Ltd., Nagoya, Japan), longitudinal images of the brachial artery at baseline were recorded with a stereotactic arm, which was used for optimal transducer positioning on the brachial artery proximal to the bifurcation of the radial and ulnar arteries, and measurements of brachial artery diameter were made after supine rest for at least 5 min. The diameter of the artery was measured from clear anterior (media–adventitia) and posterior (intima–media) interfaces, which were manually determined. Then suprasystolic compression (50 mmHg above systolic blood pressure) was performed at the right forearm for 5 min, and measurements of brachial artery diameter were made continuously from 30 s before to at least 2 min after cuff release. After at least 10 min of rest from FMD measurement, brachial artery diameter at baseline and for 5 min after administration of sublingual nitroglycerin 0.3 mg was also measured. Maximum vasodilation was then evaluated from the change in artery diameter after release of occlusion (%FMD) and after administration of nitroglycerin (%NMD).

2.4. Statistical analysis

Sample size was determined on the basis of the estimated FMD reported in other recent studies [16]. We assumed that the mean improvement in postprandial %FMD was 2.7% and the standard deviation (SD) was 2.0%. For using a two-sided test for differences, a minimal sample size of 10 patients was required in each group to detect statistical differences in %FMD with a power of 80% and an α-type error of 5% in statistical analysis. Results are expressed as means $\pm$ SD and data in the figure are presented as means $\pm$ standard error (SE). Categorical variables were compared using the chi-square test or Fisher's exact test. The two groups were compared using the Mann–Whitney *U*-test. Differences in lipid profile and endothelial function before and after 4 weeks in the two groups were compared using the Wilcoxon signed-ranks test. Pearson correlation coefficients were used to assess the relationships between maximum reduction in postpran-

Table 1
Baseline clinical characteristics.

	Total ($n=20$)	Ezetimibe ($n=10$)	Control ($n=10$)	P
Age (years)	38 ± 8	37 ± 4	38 ± 10	0.85
Male	17 (85)	9 (90)	8 (80)	0.71
BMI (kg/m^2)	24.6 ± 4.1	25.3 ± 5.2	23.9 ± 2.8	0.82
Waist circumference (cm)	87.3 ± 8.5	88.1 ± 9.4	86.5 ± 8.0	0.91
Systolic blood pressure (mmHg)	120 ± 11	122 ± 10	117 ± 11	0.16
Diastolic blood pressure (mmHg)	68 ± 7	69 ± 9	67 ± 5	0.45
Heart rate (beats/min)	64 ± 7	65 ± 9	63 ± 6	0.62
Current smoker	5 (25)	2 (20)	3 (30)	0.71
Previous smoker	6 (30)	2 (20)	4 (40)	0.45
Dyslipidemia	9 (45)	5 (50)	4 (40)	0.71
Glucose intolerance	3 (15)	2 (20)	1 (10)	0.71
Metabolic syndrome	1 (5)	0 (0)	1 (10)	0.71

Data are expressed as mean ± SD or n (%). BMI indicates body mass index.

dial %FMD and lipid profiles. Values of $P<0.05$ were considered significant.

3. Results

3.1. Postprandial lipid profiles and endothelial function

Postprandial changes in vital signs, lipid profile and endothelial function before treatment in all 20 subjects are shown in supplementary table (see supplementary data 1). Postprandial serum levels of TG, RLP-C and apoB-48 increased significantly and reached peak levels at the 4th hour (TG: from 115 ± 42 to 240 ± 115 mg/dl; RLP-C: from 5.1 ± 1.8 to 11.7 ± 6.1 mg/dl; apoB-48: from 4.5 ± 2.4 to 9.4 ± 3.8 μg/ml; fasting vs. at 4 h, all $P<0.0001$) and returned to baseline at the 8th hour. Postprandial plasma glucose levels also increased significantly at the 2nd hour (from 92 ± 11 to 113 ± 38 mg/dl, fasting vs. at 2 h, $P<0.005$) and returned to baseline at the 6th hour. In contrast, serum levels of Total-C, LDL-C and MDA-LDL significantly decreased in the postprandial state. Regarding endothelial function, postprandial %FMD decreased significantly and reached the lowest level at the 4th hour (from 8.5 ± 2.1 to 6.0 ± 2.1%, fasting vs. at 4 h, $P<0.0001$) and still remained slightly decreased value at the 8th hour (fasting vs. at 8 h, $P<0.05$). Linear regression analysis revealed that the maximum reduction in postprandial %FMD was significantly associated with the maximum increases in postprandial TG and apoB-48 concentrations (TG: $r=-0.499$, $P<0.05$; RLP-C: $r=-0.410$, $P=0.07$; apoB-48: $r=-0.551$, $P<0.05$; glucose: $r=-0.053$, $P=0.82$).

3.2. Effects of ezetimibe on fasting lipid profiles and endothelial function

Comparison of baseline characteristics in the ezetimibe and control groups is shown in Table 1. No statistically significant differences in clinical characteristics were found between the two groups. During the study, no adverse events occurred and all subjects were available for analysis. Table 2 shows the differences in fasting lipid profile and endothelial function before and after treatment for 4 weeks in the ezetimibe and control groups. Before treatment, laboratory profile and endothelial function assessed by %FMD and %NMD did not differ between the two groups. In the ezetimibe group, fasting levels of Total-C, LDL-C, MDA-LDL, TG, RLP-C and apoB-48 decreased significantly after treatment for 4 weeks, but lipid profile was not changed after 4 weeks in the control group. Among fasting laboratory data after treatment for 4 weeks, serum LDL-C and apoB-48 concentrations were significantly lower in the ezetimibe group than those in the control group. With regard to endothelial function during a fasting state, there was no significant difference between %FMD before treatment and that after treatment for 4 weeks in the ezetimibe group ($P=0.11$) and there was no significant difference

Table 2
Laboratory data and endothelial function during a fasting state before and after treatment for 4 weeks in the ezetimibe and control groups.

Variables	Ezetimibe ($n=10$)			Control ($n=10$)		
	Before	After 4 weeks	P	Before	After 4 weeks	P
Laboratory data						
Total-C (mg/dl)	225 ± 25	184 ± 28	<0.01	208 ± 10	199 ± 13	0.09
LDL-C (mg/dl)	135 ± 20	97 ± 20*	<0.01	128 ± 14	118 ± 20	0.09
HDL-C (mg/dl)	61 ± 12	61 ± 10	0.92	56 ± 17	58 ± 19	0.48
MDA-LDL cholesterol (U/l)	134 ± 23	92 ± 21	<0.01	122 ± 21	115 ± 29	0.34
TG (mg/dl)	116 ± 43	89 ± 25	<0.05	113 ± 44	109 ± 58	0.89
RLP-C (mg/dl)	5.2 ± 1.8	3.8 ± 1.3	<0.05	5.1 ± 1.9	4.5 ± 1.6	0.17
apoB-48 (μg/ml)	4.5 ± 2.9	2.4 ± 1.3*	<0.01	4.4 ± 1.9	3.8 ± 1.0	0.33
Adiponectin (μg/ml)	6.9 ± 2.0	6.8 ± 1.6	0.31	6.2 ± 3.9	6.2 ± 3.2	0.73
Blood glucose (mg/dl)	90 ± 11	93 ± 9	0.08	94 ± 11	94 ± 10	0.80
Insulin (μIU/ml)	8.0 ± 5.5	6.7 ± 3.9	0.14	6.1 ± 2.2	6.5 ± 2.1	0.26
HOMA-IR	1.8 ± 1.2	1.6 ± 0.9	0.24	1.5 ± 0.7	1.5 ± 0.7	0.44
HbA1c (%)	5.0 ± 0.1	5.0 ± 0.1	0.81	5.0 ± 0.5	4.9 ± 0.5	0.08
MCP-1 (pg/ml)	402 ± 521	381 ± 511	0.07	213 ± 51	198 ± 38	0.29
Endothelial function						
Brachial artery diameter (mm)	4.01 ± 0.70	4.04 ± 0.58	0.48	3.83 ± 0.66	3.93 ± 0.64	0.17
%FMD	8.4 ± 1.9	9.2 ± 2.3	0.11	8.5 ± 2.5	7.9 ± 1.9	0.19
%NMD	19.8 ± 5.8	19.4 ± 4.3	0.67	21.9 ± 6.8	20.9 ± 3.0	0.68

Data are expressed as mean ± SD. Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MDA, malondialdehyde; TG, triglyceride; RLP-C, remnant lipoprotein cholesterol; apoB-48, apolipoprotein B-48; HOMA-IR, homeostasis model assessment of insulin resistance; MCP, monocyte chemotactic protein; FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation.

* $P<0.05$, vs. control group after treatment for 4 weeks.

in %FMD between the two groups after treatment for 4 weeks ($P = 0.31$).

3.3. Effects of ezetimibe on postprandial lipid profiles and endothelial function

Comparison of postprandial lipid profiles and endothelial function before and after treatment for 4 weeks in the ezetimibe and control groups is shown in supplementary table (see supplementary data 2). Before treatment, postprandial lipid profiles and endothelial function did not differ between the two groups. After treatment for 4 weeks, the AUC of Total-C, LDL-C and MDA-LDL between 0 and 8 h decreased significantly in the ezetimibe group than those in the control group. Fig. 1 shows the changes in postprandial TRLs and %FMD before and after treatment for 4 weeks in the two groups. Postprandial serum TG, RLP-C and apoB-48 concentrations also decreased significantly in the ezetimibe group (AUC of TG: from 1419 ± 594 to 968 ± 321 mg h/dl, $P < 0.05$; RLP-C: from 66.9 ± 27.6 to 38.9 ± 15.4 mg h/dl, $P < 0.01$; apoB-48: from 58.8 ± 27.5 to 36.2 ± 17.0 μg h/ml, $P < 0.05$), whereas no significant changes were observed in the control group (Fig. 1A–C). Regarding postprandial endothelial function, decrease in postprandial %FMD in the ezetimibe group was suppressed significantly after 4 weeks (from $9.2 \pm 2.3\%$ to $8.1 \pm 2.3\%$ at the 4th hour), whereas decrease in postprandial %FMD in the control group after 4 weeks was almost in the same range as that before treatment (from $7.9 \pm 1.9\%$ to $5.7 \pm 2.0\%$ at the 4th hour) (Fig. 1D). The maximum change in postprandial %FMD decreased significantly after 4 weeks in the ezetimibe group (from $-2.6 \pm 1.1\%$ to $-1.2 \pm 0.8\%$, $P < 0.05$) but not different in the control group (from $-2.5 \pm 0.4\%$ to $-2.3 \pm 1.0\%$, $P = 0.14$) (Fig. 1D).

4. Discussion

In the present study, postprandial hyperlipemia induced by a conventional oral cookie loading test, a real-life situation of ingestion of dietary fat, was shown to be closely related to transient postprandial endothelial dysfunction. To the best of our knowledge, the present study is the first study showing that ezetimibe monotherapy improves postprandial hyperlipemia-induced endothelial dysfunction.

Methods for measuring apoB-48, a specific marker of intestinal lipoproteins, have recently been developed, and these methods have enabled analysis of the particle numbers of exogenous lipoproteins. Several studies have demonstrated that fasting and postprandial apoB-48 levels were significantly higher in obese and hyperlipidemic subjects or in subjects with metabolic syndrome [17]. Moreover, impaired postprandial metabolism of apoB-48 has been shown to lead to atherosclerosis in rats with metabolic syndrome [18]. Cohn et al. demonstrated that postprandial increase in TRL-TG level was mainly due to an increase in apoB48-containing TRL in normolipidemic male subjects, indicating that intestinal lipoproteins containing apoB-48 may predominantly contribute to postprandial atherogenic conditions [19]. In fact, strong relationships were observed between postprandial TG, apoB-48 increase and FMD impairment in the present study. These findings are of considerable interest, since one could argue that exogenous TG-rich lipoproteins may play a dominant role in the pathogenesis of postprandial endothelial dysfunction.

An oral cookie loading test induces not only hyperlipemia but also hyperglycemia. Postprandial hyperglycemia also induces endothelial dysfunction, especially in patients with diabetes or glucose intolerance, and increase in glucose level (glucose spike) is closely associated with impairment of postprandial endothelial function [20,21]. It has been shown that secretion of insulin induced by postprandial hyperglycemia stimulates synthesis of endothelin-1, a central vasoconstrictive hormone, and reduces nitric oxide production [22]. The present study revealed close correlation between postprandial FMD impairment and increase in postprandial TRLs, but not glucose. This observation might be due to the enrolled subjects, among which only 3 subjects had glucose intolerance, and indicates the possibility that postprandial hyperlipemia occurs more commonly than postprandial hyperglycemia in general populations in daily life.

As was found in a previous study [10], our study showed that ezetimibe decreases fasting and postprandial TG, RLP-C and apoB-48 levels after the fat loading test. Tremblay et al. investigated the effect of ezetimibe on apolipoprotein-B metabolism and showed that ezetimibe decreases the levels of TRL apoB-48 by reduction in the intestinal secretion of TRL apoB-48 in male subjects with mixed hyperlipemia [23]. Additionally, the molecular mechanisms of ezetimibe-induced attenuation of postprandial hyperlipemia have recently been elucidated by using mouse models of metabolic syndrome in which ezetimibe inhibits not only cholesterol absorption but also uptake, intracellular trafficking and metabolism of long-chain fatty acids in enterocytes, resulting in reduction of the formation of TG and apoB-48-containing lipoproteins in the small intestine [24]. These findings support our concept that ezetimibe markedly decreases the levels of postprandial TRLs, resulting in prevention of postprandial lipemia-induced endothelial dysfunction.

Only one previous study by Olijhoek et al. showed that combination therapy with low-dose simvastatin and ezetimibe preserved post-fat load endothelial function contrary to high-dose simvastatin monotherapy in male metabolic syndrome patients [16]. The present study is the first study to demonstrate that ezetimibe monotherapy preserved post-fat load endothelial function in a general population. Several studies have been performed to examine the effects of lipid-lowering drugs including statins and fibrates on postprandial hyperlipemia [25] and lipemia-induced endothelial dysfunction [26,27]. Most of those studies showed that both statins and fibrates have beneficial effects on postprandial hyperlipemia and lipemia-induced endothelial dysfunction, possibly due to direct anti-inflammatory and anti-oxidant effects as well as the lipid-lowering actions of the drugs. In some previous studies, it has been shown that ezetimibe monotherapy or combination therapy with a statin also reduces inflammatory and oxidative stress markers [28,29]. In addition, in an animal study using apoE knockout mice, ezetimibe has been shown to increase the production of endothelial nitric oxide synthase (eNOS) and decrease the production of interleukin-6, resulting in improvement of endothelial function [30]. In the present study, we did not examine the effect of ezetimibe on postprandial inflammatory or oxidative status. Moreover, we did not make a direct comparison between ezetimibe and other lipid-lowering agents. Therefore, we could not conclude whether the beneficial effects of ezetimibe on postprandial hyperlipemia and lipemia-induced endothelial dysfunction surpass the effects of other lipid-lowering agents and whether the administration of ezetimibe improves postprandial inflammation and oxidative stress. However, its lipid-lowering action may be one of the potential mechanisms by which ezetimibe improves postprandial endothelial dysfunction. Our findings support the concept that beneficial effects of ezetimibe on postprandial hyperlipemia and lipemia-induced endothelial dysfunction will prevent or delay the development of atherosclerosis. Further large-scale, prospective trials are needed to assess the relationship between the lipid-lowering effect of ezetimibe on postprandial hyperlipemia and the incidence of future cardiovascular events.

4.1. Study limitations

There are several important limitations of our study. First, this study was open-label study and the number of subjects enrolled

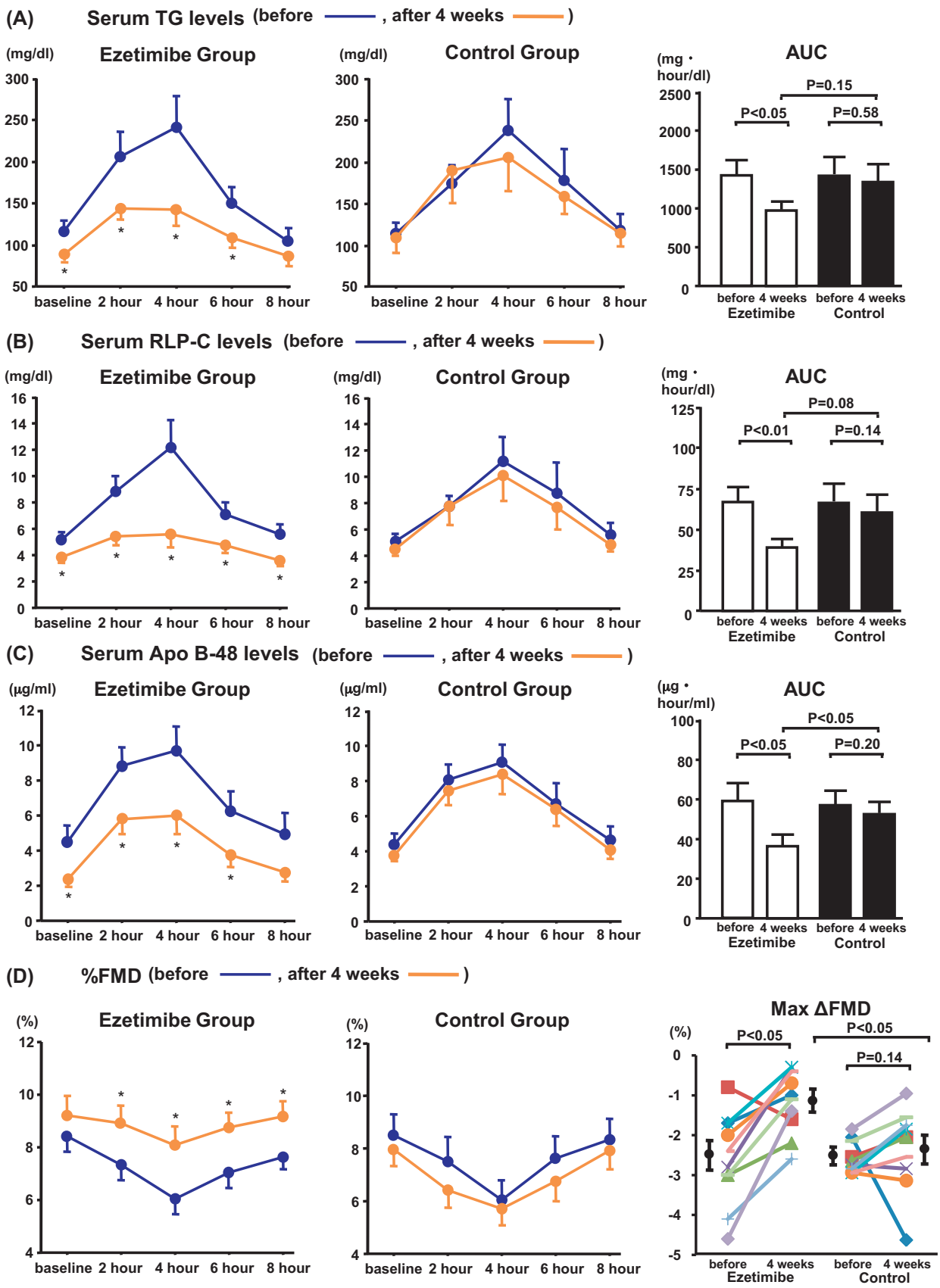

Fig. 1. (A–C) Postprandial changes in serum TG, RLP-C and apoB-48 levels and the AUC for postprandial serum TG, RLP-C and apoB-48 levels before and after treatment for 4 weeks in the ezetimibe and control groups (*open bar* indicates ezetimibe group; *solid bar*, control group). (D) Postprandial changes in %FMD and changes in maximum reduction of %FMD after the cookie test (max Δ%FMD) before and after treatment for 4 weeks in the ezetimibe and control groups. Data are expressed as mean ± SE. $^{*}P < 0.05$, vs. before treatment.

in our study was small, therefore a degree of selection bias might have occurred. Second, we did not examine postprandial insulin concentrations or postprandial inflammatory and oxidative stress status, which are well known to affect eNOS transcription and/or the release of vasoconstrictive mediators, resulting in endothelial dysfunction. Meal absorption is a complex phenomenon that involves the interaction of many factors; therefore, these parameters may need to be measured to improve test reliability and to establish the efficacy of ezetimibe for postprandial status. Third, a method for assessment of postprandial hyperlipemia has not been established, and various fat loading tests, such as oral fat meal, fat cream intake and intravenous fat load, have been performed in previous studies. Cookies are considered as a natural daily food or meal. Moreover, it has been shown by Harano et al. that the cookie test provided sufficient information about glucose intolerance and postprandial hyperlipemia [13]. Thus the oral cookie loading test with a definite quantity of fat per body surface area may be a reliable method for detecting postprandial metabolic disturbances.

5. Conclusions

The present study demonstrated that postprandial hyperlipemia is significantly associated with transient endothelial dysfunction and clearly showed that ezetimibe improves postprandial hyperlipemia and lipemia-induced endothelial dysfunction. Measurements of postprandial parameters may be useful and reliable for selecting patients with postprandial metabolic disturbances, and ezetimibe may be a potent agent for improving postprandial hyperlipemia.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.04.019.

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